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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,008	05/06/2002	Steven K Libutti	14014.0322U2	3848

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EXAMINER	
BURKHART, MICHAEL D	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/031,008	LIBUTTI ET AL.	
	Examiner	Art Unit	
	Michael D. Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/14/2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-19,21-37,39 and 40* is/are pending in the application.

4a) Of the above claim(s) *3, 5-15, 17, 19, 23-37 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 4, 16, 18, 21, 22 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/14/2007 has been entered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 2, 4, 16, 18, 21, 22 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al (U.S. patent 6,638,502, of record) in view of Restifo et al (U.S. patent

5,733,548, of record). **This rejection is maintained for reasons made of record in the Office Actions dated 2/22/2006, 11/9/2006, 6/13/2007, and for reasons set forth below.**

Regarding the new limitation in claim 40 that systemic delivery of the claimed compound results in increased levels of the antiangiogenic protein and inhibition of tumor growth, this is an intended use limitation. Such limitations in a claim to a compound do not necessarily place limits on the structure of a compound, only the structure implied by the steps. See MPEP §2111.02 (II). Because the structure taught by the prior art could be used for the intended use of systemic delivery, it is considered that the prior art structure meets the claim limitations. Furthermore, the prior art indicates that delivering antiangiogenic proteins using adenoviral vectors results in the limitations set forth by the intended use phrase. See, for example, the results of Griscelli et al (1998, of record).

Response to Arguments

Applicant's arguments filed 12/14/2007 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) Restifo et al does not present a reasonable expectation for success for the generic suggestion that the E19 signal sequence could direct secretion of a protein of from 5 to 1000 amino acids, let alone an antiangiogenic protein; 2) Restifo et al is not a scientific publication and does not claim the cited range, thus there is no presumption of scientific validity and no scientific basis for the disclosure of Restifo et al; 3) the Declaration of Dr. Renata Pasqualini (the Pasqualini declaration hereinafter) indicates that it is Dr. Pasqualini's belief that one of skill in the art would not have considered linking the results of Li et al and Restifo et al; 4) the Pasqualini declaration provides Dr. Pasqualini's opinion that those of skill in the art would not view the results of Restifo et al as providing a reasonable

expectation that the E19 signal sequence (E19 ss) could drive expression of an antiangiogenic protein, primarily because of the use of the E19 ss to express only small peptides in Restifo et al; 5) the signal sequences used by Li et al are not adenoviral signal sequences; 6) the Pasqualini declaration and applicants repeatedly assert that the signal sequences of Li et al (and Griscelli et al) are only those associated "naturally" with antiangiogenic proteins, thus, there is no expectation of success when using a heterologous signal sequence such as the E19 ss; 7) the general disclosure of signal sequences by Li et al provides no guidance as to what signal sequence could be used to express an antiangiogenic protein; 8) there is no suggestion in the art of record that an E19 ss could be used to express an antiangiogenic protein with the instantly claimed properties of increased levels of the protein and of treating tumors via systemic delivery; 9) the Pasqualini declaration indicates that the results of Libutti et al have been lauded by others as promising; 10) the Pasqualini declaration states that: until the development of the claimed constructs, nobody had been able to treat tumors both systemically and by implantation; the circulating levels achieved by Dr. Libutti were unprecedented, and effective for treating cancer patients.

Regarding 1), 2), 4), 6), and 7) prior art is presumed to be enabling, absent evidence to the contrary, not unsupported assertions or opinions, see MPEP 2121. Applicants present no reasoning or evidence, other than that the E19 ss was used by Restifo et al to express only small peptides, as to why expression of a heterologous polypeptide using the E19 ss would be unexpected. Indeed, the signal sequence naturally directs the expression of a 19 kD protein, (hence the name E19) in eukaryotic cells. Furthermore, a review of signal sequences (Martoglio

et al, 1998) teaches the conserved characteristics of signal sequences (and the machinery that recognizes them) across eukaryotic cells. Significantly, Martoglio et al teach that:

> "Different signal sequences guide their passenger proteins through apparently common pathways and can be interchanged between different proteins or even between proteins of different organisms." See page 410, second column, second full ¶.

The prior art clearly indicates that the E19 ss is functional to direct the secretion of heterologous proteins/peptides. Thus given the teachings of the prior art, one of skill in the art could predictably use this signal sequence to direct secretion of antiangiogenic proteins from an adenoviral vector in a eukaryotic cell. These teachings of the prior art rebut any assertions or opinions by applicants, or found in the Pasqualini declaration, that the skilled artisan could not have used the E19 ss to express an antiangiogenic protein in a predictable manner. Furthermore, the totality of the prior art teaches that antiangiogenic proteins can be expressed using signal sequences other than those "naturally" associated with the antiangiogenic protein.

Regarding 3), opinion evidence on the ultimate legal issue is not persuasive. See MPEP §716.01 (III).

Regarding 1), 2), 4), 5) and 6) in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Further regarding 6) and 7), there are no teachings in any of the references made of record that the expression and secretion of an antiangiogenic protein must be done using a signal sequence "naturally" associated with the protein. Applicants do not explain how the other

antiangiogenic proteins (e.g. endostatin) disclosed by Li et al are to be expressed if not associated with a heterologous signal sequence. Indeed, Applicants Exhibit C, submitted with the Pasqualini declaration, teaches that endostatin is a cleavage product and lacks a secretion signal. Hence, one must be provided for it that is not "naturally" associated with endostatin. Finally, the functional expression and secretion of angiostatin and endostatin by heterologous signal peptides has been demonstrated in the prior art. See U.S. Patent 6,475,784 (expression of angiostatin using the IgK signal peptide) and U.S. Patent 6,797, 488 (expression of endostatin using the yeast alpha factor signal peptide).

Regarding 8), this intended use limitation has been addressed above. Furthermore, absent evidence to the contrary, the use of the adenoviral E19 ss sequence to express an antiangiogenic protein in the context of an adenoviral vector would result in increased levels of circulating antiangiogenic protein relative to organisms/animals that did not receive the adenoviral vector, or received a control vector not expressing the antiangiogenic protein. Finally, all of the evidence in the prior art suggests that the use of such vectors can lead to an inhibition of tumor growth. See the results of Griscelli et al mentioned above, and those mentioned in Exhibit C (submitted with the Pasqualini declaration), page 1018, third column, first full ¶.

Regarding 9) and 10), the evidence relied upon does not fall within the scope of the claimed, elected invention, which is directed to adenoviral vectors. In Exhibit C, the vector used was a retrovirus, and there is no mention of systemic administration of the retroviral vector, as required by the instant claims. Cells infected *ex vivo* with the retroviral vector were implanted into mice. Thus, any surprising or laudable results from this publication cannot be extended to the instantly claimed compositions.

Response to Amendment

The declaration under 37 CFR 1.132 filed 12/14/2007 is insufficient to overcome the rejection of claims 2, 4, 16, 18, 21, 22 and 40 based upon a rejection under 35 USC 103(a) as set forth in the last Office action because: the arguments and assertions presented in the Pasqualini Declaration are set forth and addressed above. This Declaration was unconvincing for the reasons set forth above.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael D. Burkhart
Examiner
Art Unit 1633